USE OF N-SUBSTITUTED AZAHETEROCYCLIC COMPOUNDS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INDICATIONS RELATED TO ANGIOGENESIS

FIELD OF INVENTION

The present invention relates to the use of N-substituted azaheterocyclic compounds of the general formulas Ia-Id for the treatment, prevention, alleviation or amelioration of conditions related to angiogenesis. Hence the compounds can be used in the treatment of patients suffering from a variety of diseases like abnormal tissue growth, neoplasia, hyperplasia, cancer, diabetic retinopathy. The present invention also embraces pharmaceutical compositions comprising those compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF INVENTION

Tissue growth is critically dependent upon the formation of new capillaries, called angiogenesis or neovacularisation. The process may in pathological conditions be turned on by growth factors, e.g. vascular endothelial growth factor or cytokines, e.g. tumor necosis factor α. In e.g. cancer, angiogenesis is an important factor for the maintenance and growth of the tumor (Tanaka et al., Cancer Res., 58, 3362-3369, 1998). Angiogenesis is important for neoplastic conditions like cancer as well as ocular neovascularization like diabetic retinopathy (Favard et al., Diabetes and Metabolism 22 , 268-273, 1996) . . Thus it has been shown that treatments directed against angiogenesis can e.g. inhibit tumor growth (Folkman, J., Breast Cancer Res. and Treat., 36, 190-118, 1995, Tanaka et al.,Cancer Res., 58, 3362-3369, 1998). The fact that angiogenesis is prominent in the female reproductive system suggests that treatments against angiogenesis are important for several conditions like bleeding disorders or in the context of birth control (Pepper, Arteriosclerosis, Thrombosis, and Vascular Biology 17:605-619, 1997).

Thus one object of the invention is to provide compounds which can be used in the treatment of patients suffering from diseases in which neovascularisation or angiogenesis prevails or for the control of normal angiogenesis to obtain e.g. birth control.

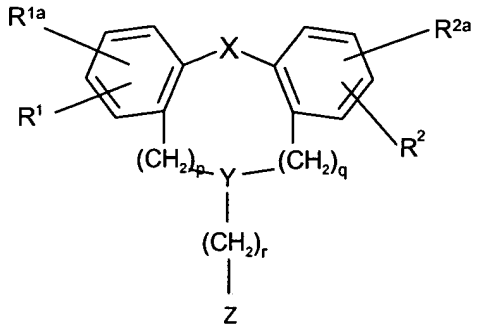
WO 9518793 discloses N-substituted azaheterocyclic carboxylic acids and esters thereof, methods for their preparation, compositions containing them and their use in treatment of hyperalgesic and/or inflammatory conditions.

WO9631497, WO9631498, WO9631499, WO9631481, WO9711071, WO9815548, WO9815546, WO9815550, PCT/DK98/00273, PCT/DK98/00271, DK 0367/98, DK 0366/98, DK 1472/97 and DK 1523/98 discloses N-substituted azaheterocyclic compounds, methods for their preparation, compositions containing them and their use in treatment of hyperalgesic and/or inflammatory conditions as well as as well as their use for treatment of indications caused by or related to the secretion and circulation of insulin antagonising peptides, e.g. non-insulin-dependent diabetes mellitus (NIDDM) and ageing-associated obesity.

DESCRIPTION OF THE INVENTION

It has surprisingly been found that compounds of the general formulas Ia-Id below can be used in the treatment, prevention, alleviation or amelioration of an indication related to angiogenesis.

Accordingly, the present invention relates to the use of a compound of the following groups of compounds having the general formula Ia



(Ia)

wherein R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, NR^7R^8, cyano, methylthio or $-SO_2NR^7R^8$ wherein $R^7$and R^8 independently are hydrogen or C_{1-6}-alkyl; and

Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; or

Y is -CH_2N(-)CH_2-, -CH_2N(-)CH_2-, -(C=O)N(-)CH_2-, -CH_2N(-)(C=O)-, -CH_2CH(-)CH_2-, -CH_2CH(-)CH_2-, -CH_2C(-)=CH-, -CH=C(-)CH_2-, -OCH(-)CH_2-, -CH_2CH(-)O-, -SCH(-)CH_2-, -CH_2CH(-)S-, wherein only the underscored atom participates in the ring system; or

Y is >N-, >CH-, >N-(C=O)- or >C=C(R^8)-, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6}-alkyl; or

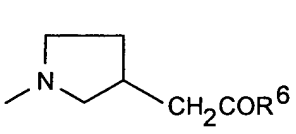
Y is >CH-O- or >CH-$S(O)_y$ wherein y is 0, 1 or 2, or -N(R^8)- wherein R^8 is hydrogen or C_{1-6}-alkyl, and wherein only the underscored atom participates in the ring system; and

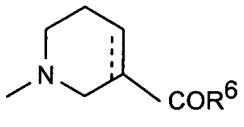
X is completion of an optional bond, ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -CH_2OCH_2-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N$(CH_3)SO_2$-, -SO_2N(CH_3)-, -CH(R^9)CH_2-, -CH_2CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q independently are 0 or 1; and

r is 0, 1, 2 , 3 or 4; and

Z is selected from

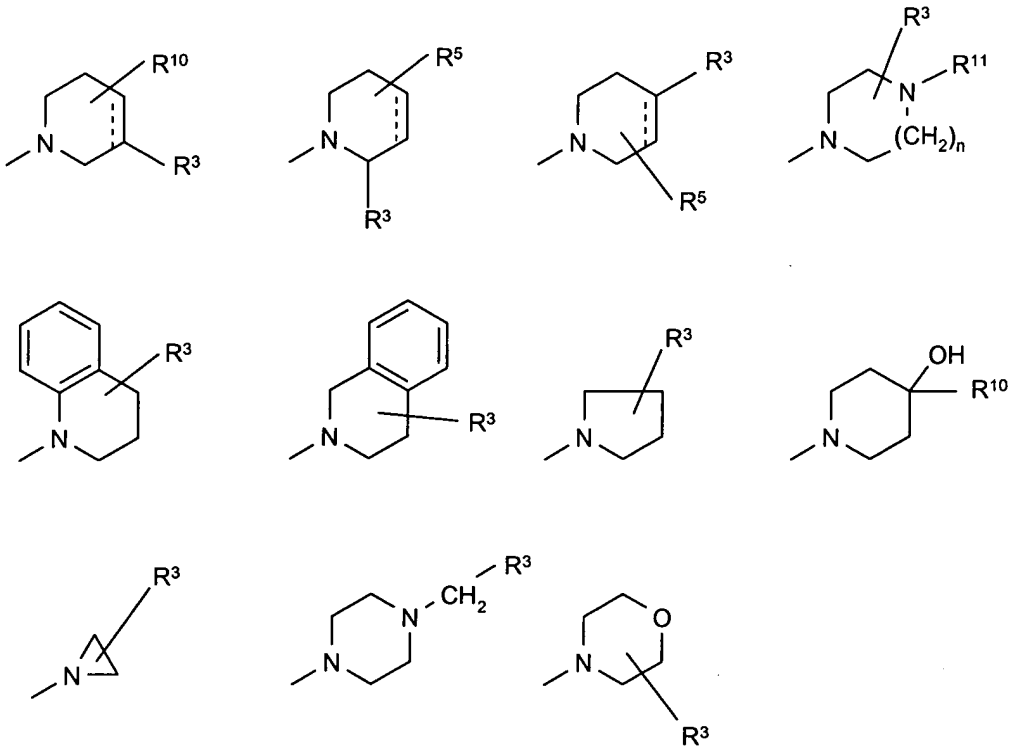




wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; or

Z is selected from



wherein n is 1 or 2;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

R^4 is -OH, $-NH_2$, -NHOH or C_{1-6}-alkoxy; and

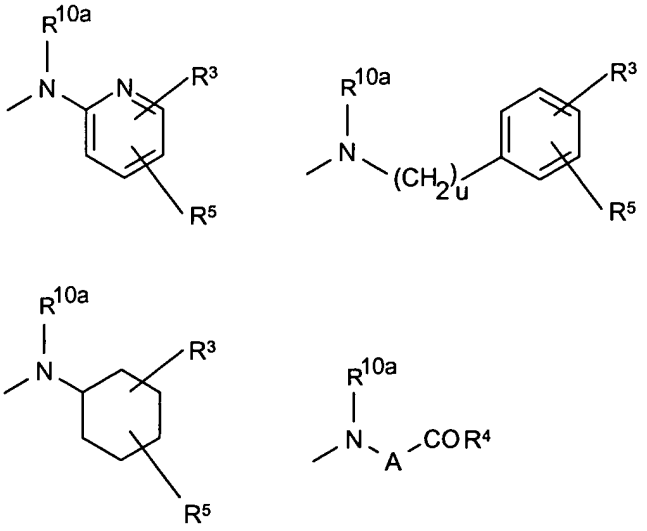
R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{11} is hydrogen or C_{1-6}-alkyl; and

.... is optionally a single bond or a double bond; or

Z is selected from



wherein u is 0 or 1;

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

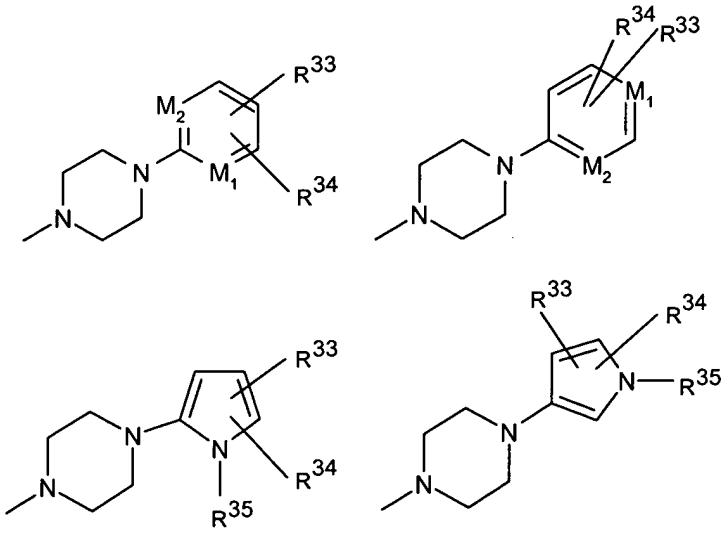
R^4 is -OH, $-NH_2$, -NHOH or C_{1-6}-alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10a} is hydrogen or C_{1-6}-alkyl; and

A is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; or

Z is selected from



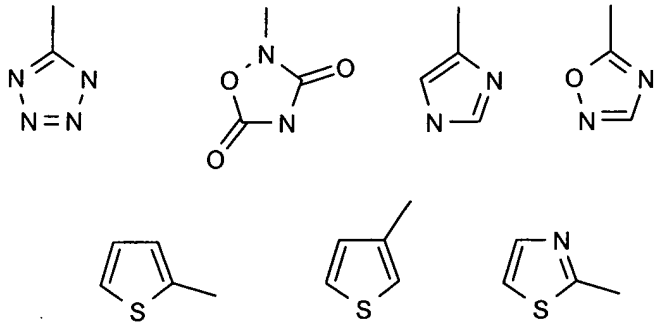
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

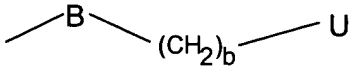
R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6}-alkoxy or NHR^{32}, wherein R^{32} is hydrogen or C_{1-6}-alkyl, and w is 0, 1 or 2; or

R^{34} is selected from



or

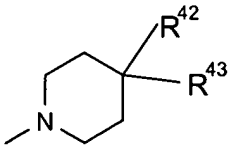
Z is



wherein b is 0, 1, 2, 3 or 4; and

B is $-CH=CR^{49}-$, $-CR^{49}=CH-$, $-C\equiv C-$, $-(C=O)-$, $-(C=CH_2)-$, $-(CR^{49}R^{40})-$, $-CH(OR^{41})-$, $-CH(NHR^{41})-$, phenylene, C_{3-7}-cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6}-unbranched alkyl, C_{3-6}-branched alkyl or C_{3-7}-cycloalkyl and wherein R^{41} is hydrogen or C_{1-6}-alkyl; and

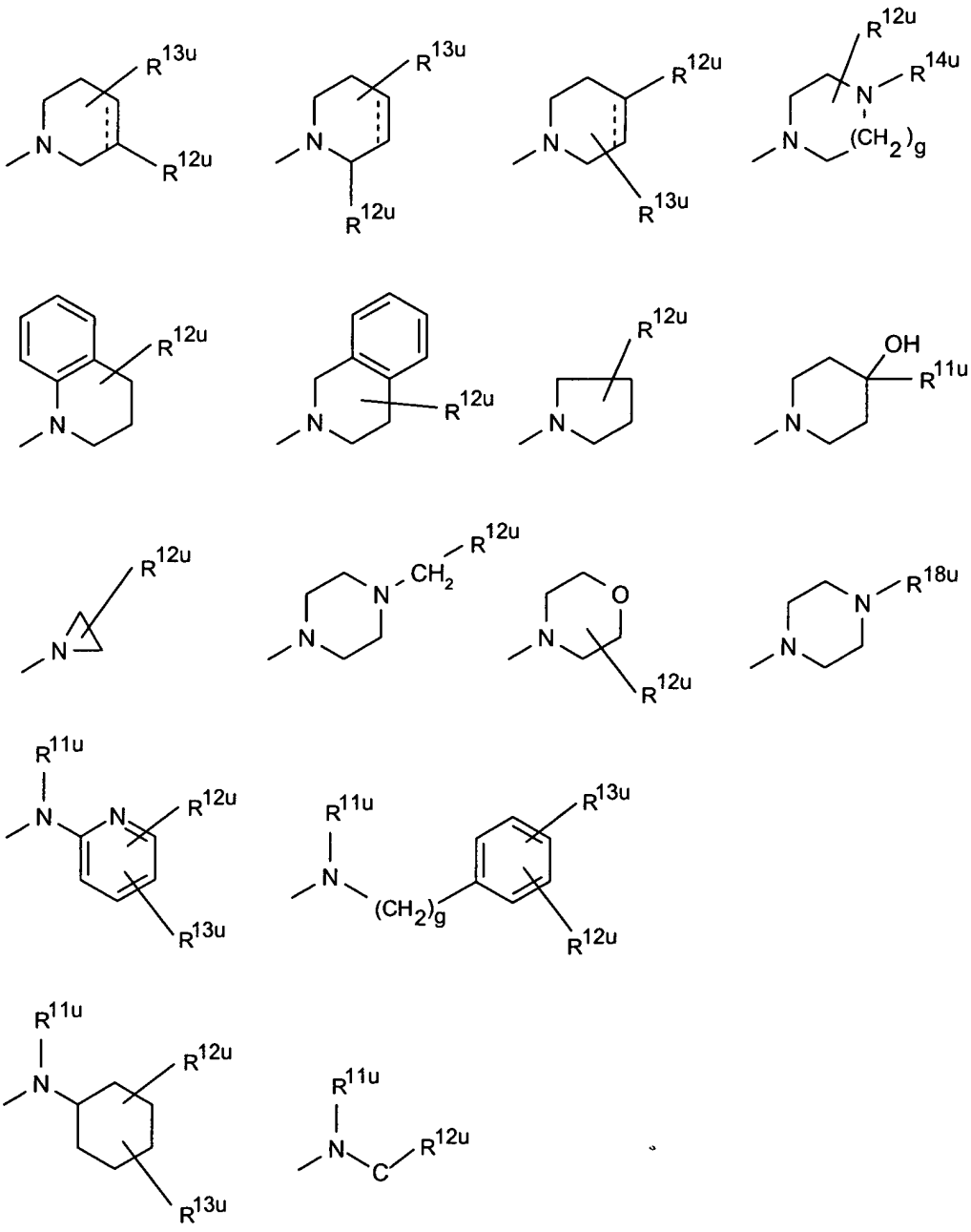
U is



wherein R^{42} is hydrogen, $-(CH_2)_cOH$ or $-(CH_2)_dCOR^{47}$ wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is -OH, $-NHR^{44}$ or C_{1-6}-alkoxy wherein R^{44} is hydrogen or C_{1-6}-alkyl; and

R^{43} is cyano, $-NR^{45}R^{46}$, $-NR^{45}$-V or $-(CHR^{48})_e$-V wherein R^{45} and R^{46} independently are hydrogen or C_{1-6}-alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen,

halogen, cyano, trifluoromethyl, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, $-NR^{45}R^{46}$ or -COOH, and wherein V is C_{3-8}-cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C_{1-6}-alkyl or C_{1-6}-alkoxy; or U is selected from



wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is -OH, $-NHR^{20u}$ or C_{1-6}-alkoxy wherein R^{20u} is hydrogen or C_{1-6}-alkyl; and

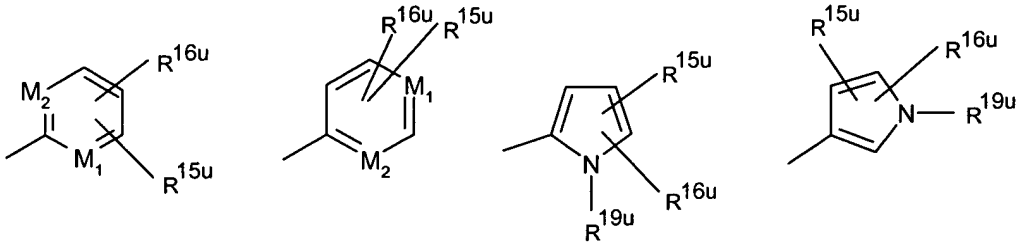
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14u} is hydrogen or C_{1-6}-alkyl; and

C is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; and

.... is optionally a single bond or a double bond; and

R^{18u} is selected from



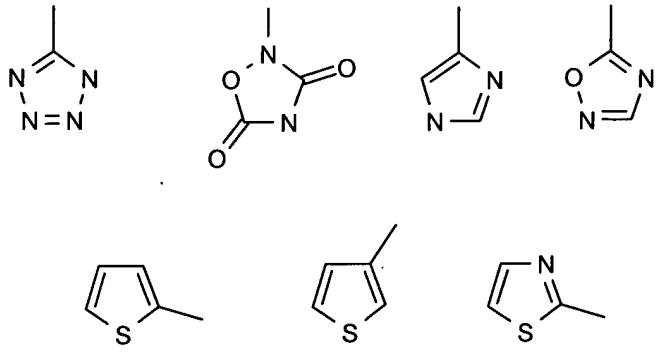
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

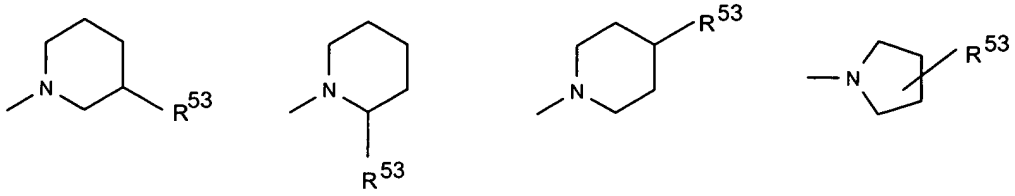
R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



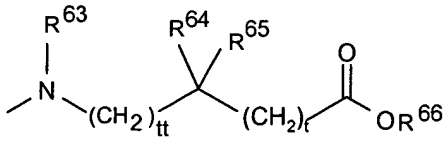
or

Z is selected from



wherein R^{53} is $-(CH_2)_{pp}COOH$ wherein pp is 2, 3, 4, 5 or 6; or

Z is



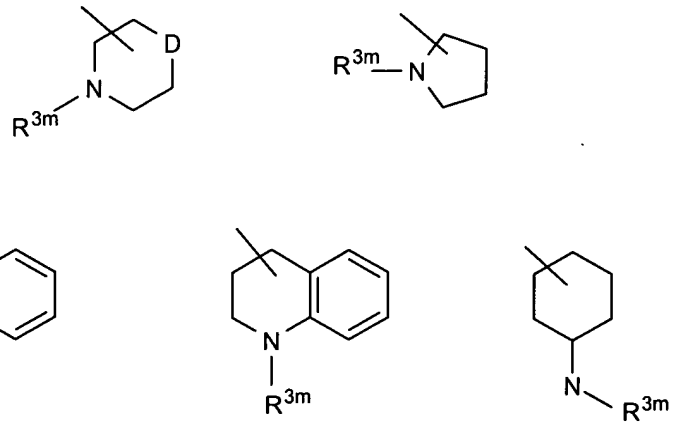
wherein tt and t independently are 0, 1 or 2; and

R^{63} is H, C_{1-6}-alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring; and

R^{66} is H or C_{1-6}-alkyl; or

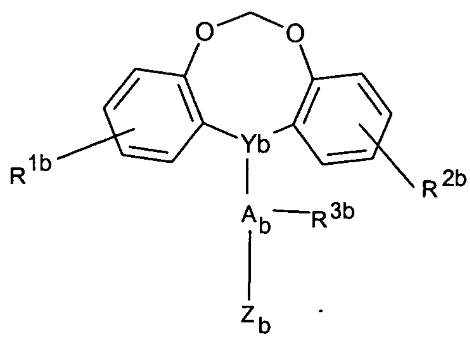
Z is selected from



wherein D is $-CH_2-$, -O-, -S- or $-N(R^7)-$ wherein R^7 is hydrogen or C_{1-6}-alkyl; and

R^{3m} is $-(CH_2)_{mm}OH$ or $-(CH_2)_{mp}COR^4$ wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

having the general formula Ib



(Ib)

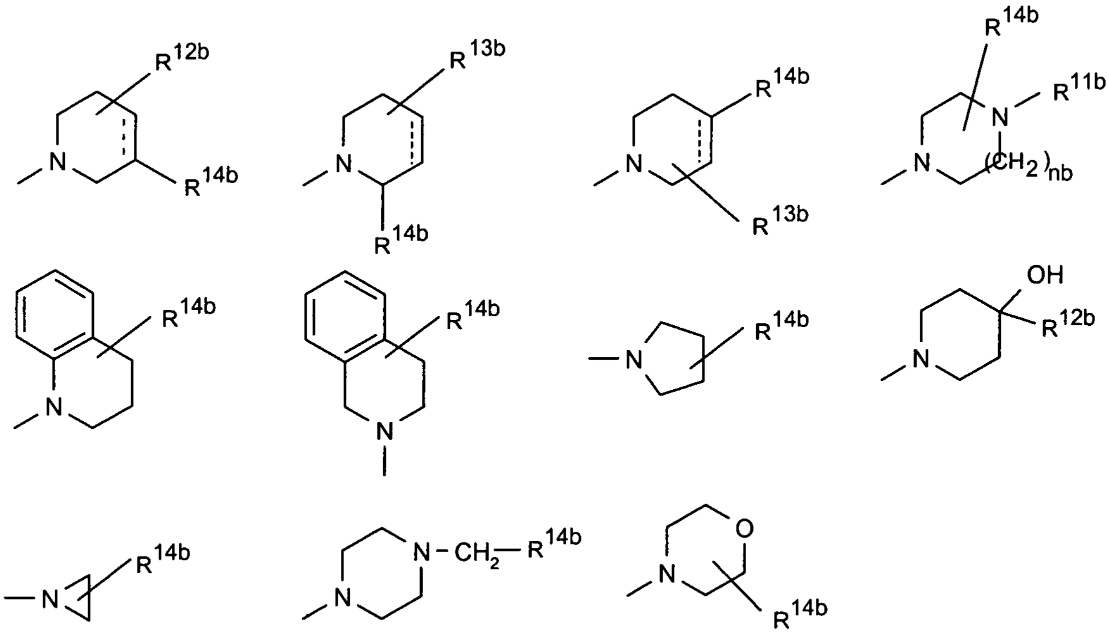
wherein R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

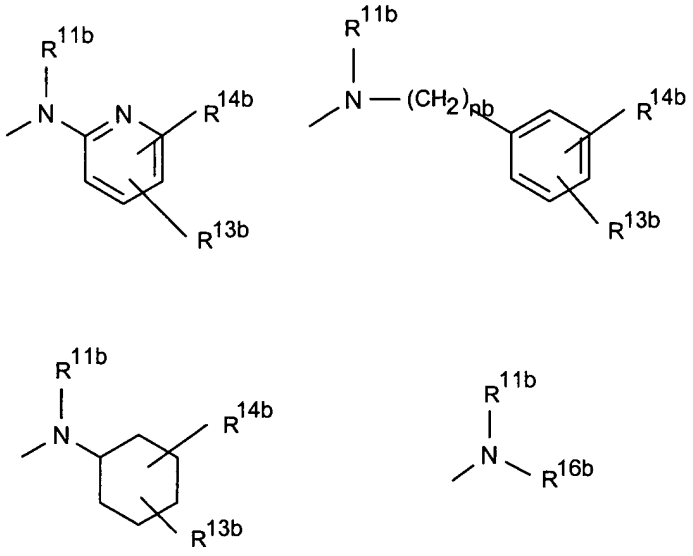
R^{3b} is hydrogen or C_{1-3}-alkyl; and

A_b is C_{1-3}-alkylene; and

Y_b is >$\underline{C}$H-CH_2-, >$\underline{C}$=CH-, >$\underline{C}$H-O-, >$\underline{C}$=N-, >$\underline{N}$-CH_2- wherein only the underscored atom participates in the ring system; and

Z_b is selected from





wherein nb is 1 or 2; and

R^{11b} is hydrogen or C_{1-6}-alkyl; and

R^{12b} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

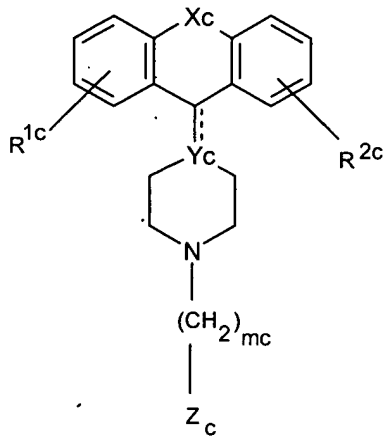
R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14b} is $-(CH_2)_{mb}OH$ or $-(CH_2)_{tb}COR^{15b}$ wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and wherein R^{15b} is -OH, NH_2, -NHOH or C_{1-6}-alkoxy; and

R^{16b} is C_{1-6}-alkyl or $-B_b-COR^{15b}$, wherein B_b is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or

having the general formula Ic



(Ic)

wherein R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy;

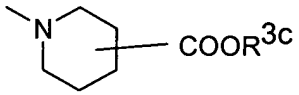
X_c is ortho-phenylene, -O-, -S-, $-C(R^{6c}R^{7c})-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-N(R^{8c})-(C=O)-$, $-(C=O)-N(R^{8c})-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^{8c})-$, $-N(R^{8c})(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10c})CH_2-$, $-CH_2CH(R^{10c})-$, $-(C=O)-$, $-N(R^{9c})-$ or -(S=O)- wherein R^{6c}, R^{7c}, R^{8c} and R^{9c} independently are hydrogen or C_{1-6}-alkyl, and wherein R^{10c} is C_{1-6}-alkyl or phenyl;

Y_c is C or N;

.... is optionally a single bond or a double bond, and .... is a single bond when Y_c is N;

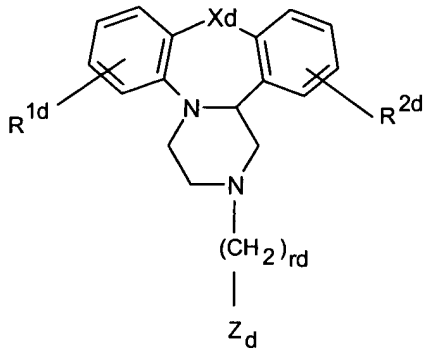
mc is 1, 2, 3, 4, 5 or 6; and

Z_c is $-COOR^{3c}$ or



wherein R^{3c} is H or C_{1-6}-alkyl; or

having the general formula Id



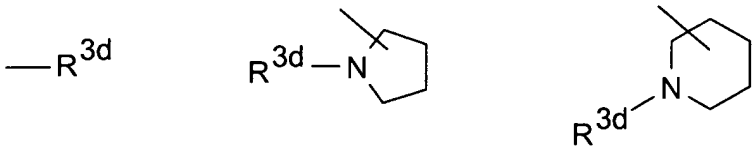
(Id)

wherein R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

rd is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ; and

Z_d is selected from



wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention, alleviation or amelioration of a condition related to angiogenesis.

The compounds according to the invention may exist as geometric and optical isomers and all isomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention. Isomers may be separated by means of standard methods such as chromatographic techniques or fractional crystallisation of suitable salts.

Preferably, the compounds according to the invention exist as the individual geometric or optical isomers.

The compounds according to the invention may optionally exist as pharmaceutically acceptable acid addition salts, metal salts or, optionally alkylated, ammonium salts.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also included are the hydrates of the above mentioned acid addition salts which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or by precipitation or crystallisation.

The compounds according to the invention may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a lower alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free base forms.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The terms "C_{1-6}-alkyl" and "C_{1-8}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 and 1 to 8 carbon atoms respectively. Examples of such groups include, but are not limited to , methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, iso-hexyl, 4-methylpentyl, neopentyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination is intended to include those C_{1-6}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked thorugh an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isoprpoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The terms "C_{3-7}-cycloalkyl" and "C_{3-8}-cycloalkyl" as used herein, represents a carbocyclic group having from 3 to 7 carbon atoms and having from 3 to 8 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The term "C_{3-7}-cycloalkylene" as used herein represents a bisubstituted carbocyclic group having from 3 to 7 carbon atoms e.g. cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene and cycloheptylene and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), phenanthrenyl, fluorenyl, indenyl and the like.

The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, quinozolinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl and the like. Heteroaryl is also intended to include the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially or fully hydrogenated derivatives are pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, diazepinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, oxazolinyl, oxazepinyl, aziridinyl and tetrahydofuranyl.

The term "3- to 8-membered carbocyclic ring" as used herein refers to a monocyclic unsaturated or saturated ring containing from 3 to 8 carbon atoms. The term includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

In a preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

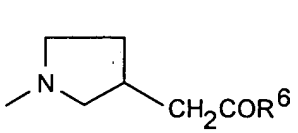
Y is >$\underline{N}$-CH_2- , >$\underline{C}$H-CH_2- or >$\underline{C}$=CH- wherein only the underscored atom participates in the ring system; and

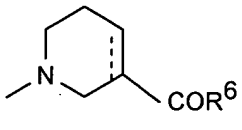
X is -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -O-CH_2-, -(C=O)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and

p and q are 0, and

r is 1, 2 or 3; and

Z is selected from





wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

Preferred compounds of the present invention include

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(Fluoren-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Thioxanthen-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-butyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-pyrrolidinacetic acid;

(R)-1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(2-Trifluoromethyl-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Oxo-10H-phenothiazin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-10-Oxa-5-aza-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1,2,5,6-tetrahydro-3-pyridinecarboxylic acid;

(R)-1-(3-(6,7-Dihydro-5H-dibenzo[b,g]azocin-12-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10-Methyl-11-oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9(H)-Oxo-10H-acridin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(2-(6,11-Dihydrodibenz[b,e]oxepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(Z)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(E)-(R)-1-(3-(2-Iodo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride;

(R)-1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid hydrochloride.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

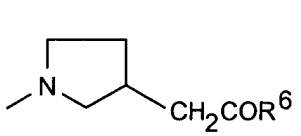
Y is -$\underline{C}H_2\underline{N}(-)CH_2$-, -$CH_2\underline{N}(-)\underline{C}H_2$-, -$(\underline{C}=O)\underline{N}(-)CH_2$-, -$CH_2\underline{N}(-)(\underline{C}=O)$-, -$\underline{C}H_2\underline{C}H(-)CH_2$-, -$CH_2\underline{C}H(-)\underline{C}H_2$-, -$\underline{C}H_2\underline{C}(-)$=CH-, -CH=$\underline{C}(-)\underline{C}H_2$-, -$\underline{OC}H(-)CH_2$-, -$CH_2\underline{C}H(-)\underline{O}$-, -$\underline{SC}H(-)CH_2$-, -$CH_2\underline{C}H(-)\underline{S}$-, wherein only the underscored atom participates in the ring system; and

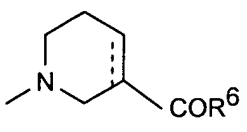
X is -O-, -S-, -$C(R^7R^8)$-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -$N(R^8)$-(C=O)-, -(C=O)-$N(R^8)$-, -O-CH_2-, -CH_2-O-, -S-CH_2-, -CH_2-S-, -$N(R^8)$-, -(C=O)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and

p and q independently are 0 or 1; and

r is 1, 2 or 3; and

Z is selected from





wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

(R)-1-(3-(6,11-Dioxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6,11-Dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5,11-Dihydro-10H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenzo[b,f][1,4]thiazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,f][1,4]oxathiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenzo[b,e][1,4]dithiepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11H-Dibenz[b,e][1,4]oxathiepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-10H-dibenz[b,g][1,5]oxazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-10H-dibenzo[b,g][1,5]thiazocin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(11,12-Dihydro-6H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(11,12-Dihydro-5H-dibenzo[a,e]cycloocten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(7,12-Dihydro-6H-dibenzo[a,d]cycloocten-6-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5-Methyl-5,11-dihydro-dibenz[b,f]azepin-10-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Oxo-5,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6-Oxo-11,12-dihydro-5H-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-dibenz[b,f][1,4]oxazepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5,6,11,12-Tetrahydro-dibenz[b,f]azocin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11-Oxo-6,11-dihydro-5H-dibenz[b,e]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-dibenz[b,f]azepin-10-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6,7-Dihydro-5H-dibenz[b,g][1,5]oxazocin-6-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(11,12-Dihydro-dibenz[a,e]cycloocten-5-yl)-1-propyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, NR^7R^8, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl ; and

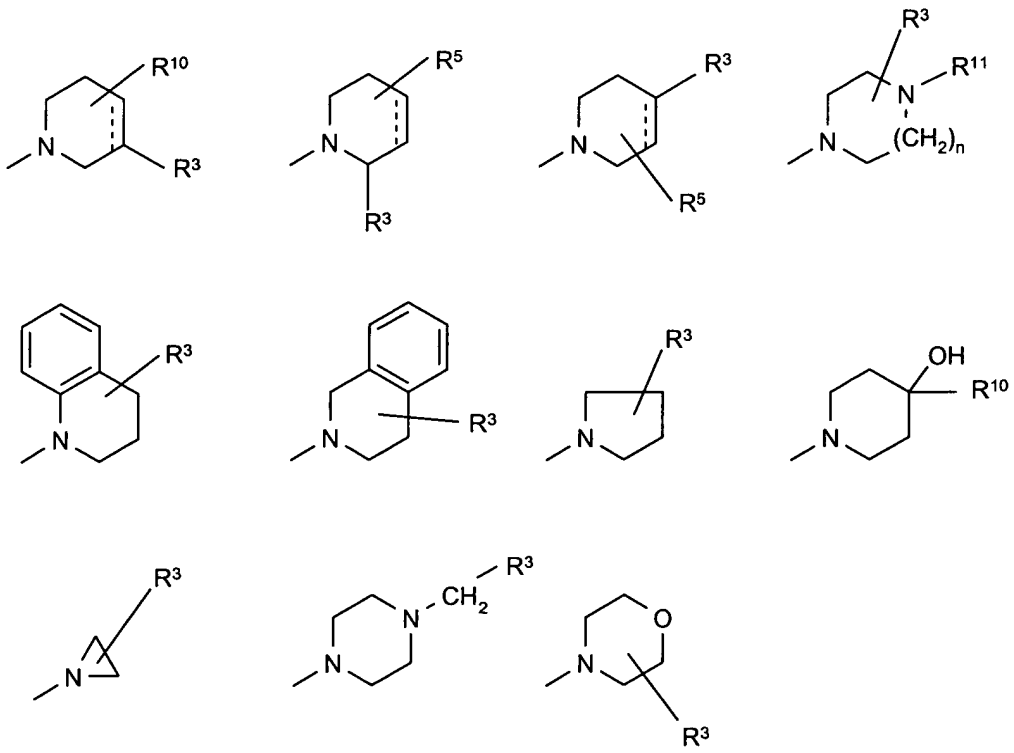
Y is >$\underline{N}$-CH_2- , >$\underline{C}$H-CH_2- or >$\underline{C}$=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -S-CH_2-, -CH_2-S-, -N(R^8)-, -(C=O)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



wherein n is 1 or 2; and

R^3 is $-(CH_2)_mOH$ or $-(CH_2)_sCOR^4$ wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein

R^4 is -OH, $-NH_2$, -NHOH or C_{1-6}-alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{11} is hydrogen or C_{1-6}-alkyl; and

.... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidine-carboxamide;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperidinecarboxylic acid;

(1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinyl)methanol;

4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinol;

4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;

(2S,4R)-1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-hydroxy-2-pyrrolidinecarboxylic acid;

4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-morpholinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-aziridinecarboxylic acid;

2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-4-isoquinolinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-methyl-[1,4]-diazepane-6-carboxylic acid;

2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid hydroxamide;

(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)piperazin-1-yl)acetic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-piperazinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidineacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxamide;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-pyrrolidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-pyrrolidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

1-(3-(10H-Phenoxazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidineacetic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-2-methyl-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-quinuclidiniumcarboxylate;

1-(3-(2,8-Dibromo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3,7-Dichloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl-4-piperidinecarboxylic acid;

1-(3-(3,7-Dimethyl-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(3-Dimethylamino-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-4-piperidine-carboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

(S)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-2-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(2-Chloro-6,11-dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-ethyl)-3-piperidinecarboxylic acid;

1-(3-(2-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-2-piperidineacetic acid;

1-(3-(Phenothiazin-10-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-2-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(6,11-Dihydrodibenzo[b,e]oxepin-11-ylidene)-1-ethyl)-4-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

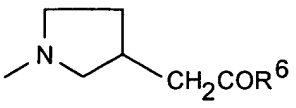
Y is >$\underline{N}$-CH_2- , >$\underline{C}$H-CH_2- or >$\underline{C}$=CH- wherein only the underscored atom participates in the ring system; and

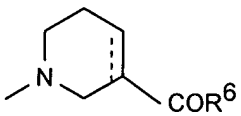
X is ortho-phenylene, -CH_2-(C=O)-, -(C=O)-CH_2-, -S-CH_2-, -CH_2-S-, -$(CH_2)N(R^8)$-, -$N(R^8)(CH_2)$-, -$N(CH_3)SO_2$-, -$SO_2N(CH_3)$-, -$CH(R^9)CH_2$- or -$CH_2CH(R^9)$- wherein R^8 is hydrogen or C_{1-6}-alkyl and R^9 is C_{1-6}-alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from





wherein R^6 is OH or C_{1-6}-alkoxy; and

.... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(9H-Tribenz[b,d,f]azepin-9-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6-Methyl-6H-dibenzo[c,f][1,2]thiazepin-5,5-dioxide-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Methyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Phenyl-10,11-dihydro-5H-dibenzo[b,e]cyclohepten-5-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(6,11-Dihydro-11H-dibenzo[b,e][1,4]thiazepin-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(10-Methyl-10,11-dihydro-dibenzo[b,e][1,4]diazepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10-Oxo-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(6-Methyl-6,11-dihydro-dibenzo[c,f][1,2,5]thiadiazepin-5,5-dioxide-11-yl)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(5-Methyl-5,6-dihydrodibenz[b,e]azepin-11-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9H-Tribenzo[a,c,e]cyclohepten-9-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(9H-Tribenzo[b,d,f]azepine-9-yl)propyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia
R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

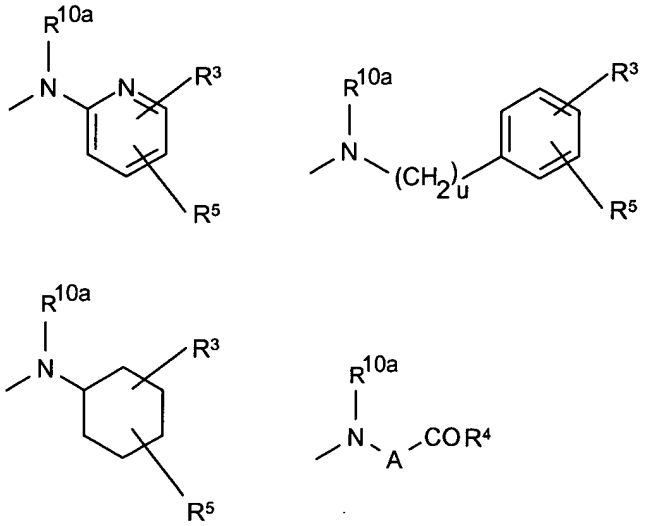
Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -S-CH_2-, -CH_2-S-, -N(R^8)-, -(C=O)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



wherein u is 0 or 1;

R^3 is -$(CH_2)_m$OH or -$(CH_2)_s$COR^4 wherein m is 0, 1, 2, 3, 4, 5 or 6 and s is 0 or 1 and wherein R^4 is -OH, -NH_2, -NHOH or C_{1-6}-alkoxy; and

R^5 is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{10a} is hydrogen or C_{1-6}-alkyl; and

A is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

3-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)propionic acid;

4-(N-Methyl-N-(3-(10,11-dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)butyric acid;

3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)propionic acid;

2-(N(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methyl-amino)succinic acid;

2-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

2-(N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)nicotinic acid;

2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)methyl)benzoic acid;

2-((N-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-N-methylamino)-1-cyclohexanecarboxylic acid;

2-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propylamino)pyridin-3-ol;

3-((3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

2-((3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid;

2-(N-(3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)amino)benzoic acid;

5-Bromo-2-(N-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)amino)benzoic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy;

Y is >N-CH_2- , >CH-CH_2- , >C=CH- or >CH-O- wherein only the underscored atom participates in the ring system; and

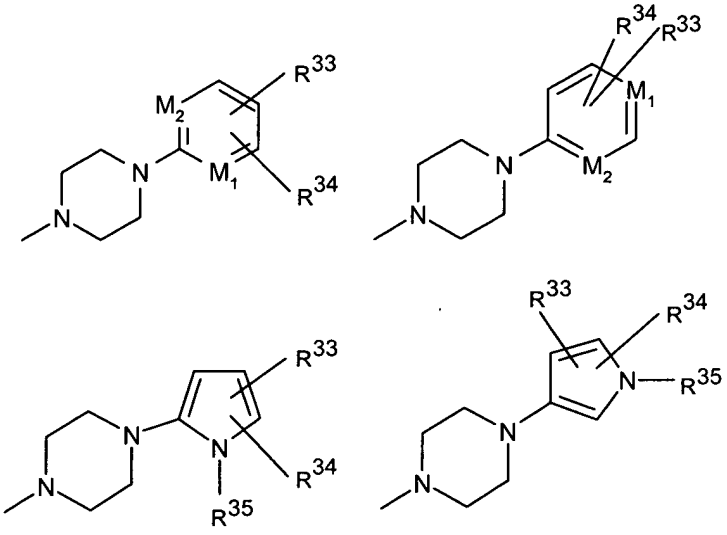
X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N(CH_3)SO_2-, -SO_2N(CH_3)-, -

$CH(R^9)CH_2$-, $-CH_2CH(R^9)$-, -(C=O)-, $-N(R^8)$- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is selected from



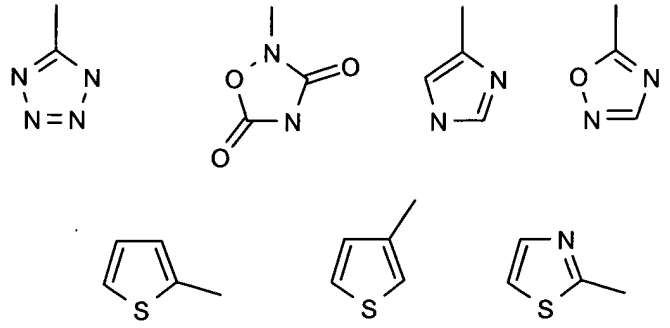
wherein M_1 and M_2 independently are C or N; and

R^{35} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{33} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{34} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_wCOR^{31}$, $-(CH_2)_wOH$ or $-(CH_2)_wSO_2R^{31}$ wherein R^{31} is hydroxy, C_{1-6}-alkoxy or NHR^{32}, wherein R^{32} is hydrogen or C_{1-6}-alkyl, and w is 0, 1 or 2; or

R^{34} is selected from



or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

2-(4-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2,10-Dichloro-12H-dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(12H-Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(2-Chloro-12H-dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-3-pyridinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-pyridyl)piperazine;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propyl)-1-piperazinyl)-3-pyridine-carboxylic acid;

2-(4-(2-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-ethyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

6-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-2-pyridinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenz[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-5-pyridinecarboxylic acid;

2-(4-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)3-pyridinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(2-nitrophenyl)-piperazine;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzonitrile;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-1-piperazinyl)-benzoic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-(3-trifluoromethyl-2-pyridyl)piperazine;

2-(4-(2-(6,11-Dihydro-dibenzo[b,e]thiepin-11-ylidene)ethyl)piperazin-1-yl)-3-pyridinecarboxylic acid;

2-(4-(3-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

2-(4-(2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)ethyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

6-(4-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperazin-1-yl)-2-pyridinecarboxylic acid;

2-(4-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-1-piperazinyl)-3-pyridinecarboxylic acid;

6-(4-(3-(Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-piperazin-1-yl)-pyridine-2-carboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

Y is >N-, >CH-, >N-(C=O)- or >C=C(R^8)-, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6}-alkyl; and

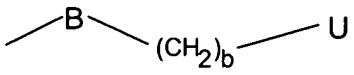
X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -CH_2OCH_2-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N$(CH_3)SO_2$-, -

$SO_2N(CH_3)$-, -$CH(R^9)CH_2$-, -$CH_2CH(R^9)$-, -(C=O)-, -$N(R^8)$- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl;

and p and q are 0; and

r is 0, 1, 2, 3 or 4; and

Z is



wherein b is 0, 1, 2, 3 or 4; and

B is -CH=CR^{49}-, -CR^{49}=CH-, -C≡C-, -(C=O)-, -(C=CH_2)-, -($CR^{49}R^{40}$)-, -$CH(OR^{41})$-, -$CH(NHR^{41})$-, phenylene, C_{3-7}-cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6}-unbranched alkyl, C_{3-6}-branched alkyl or C_{3-7}-cycloalkyl and wherein R^{41} is hydrogen or C_{1-6}-alkyl; and

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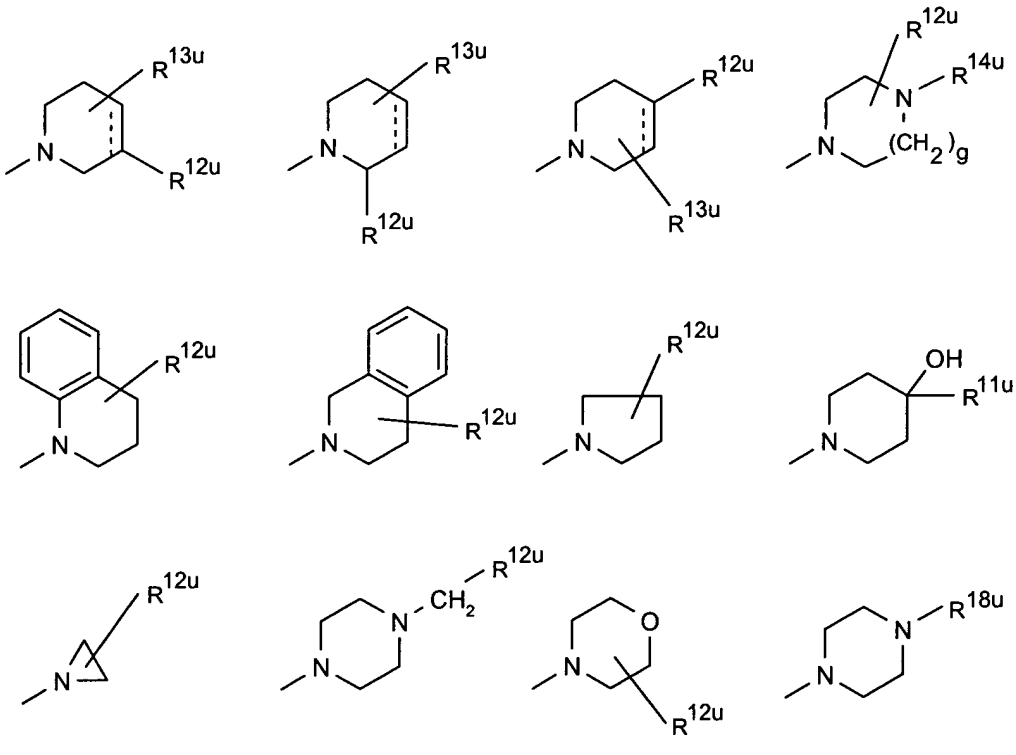
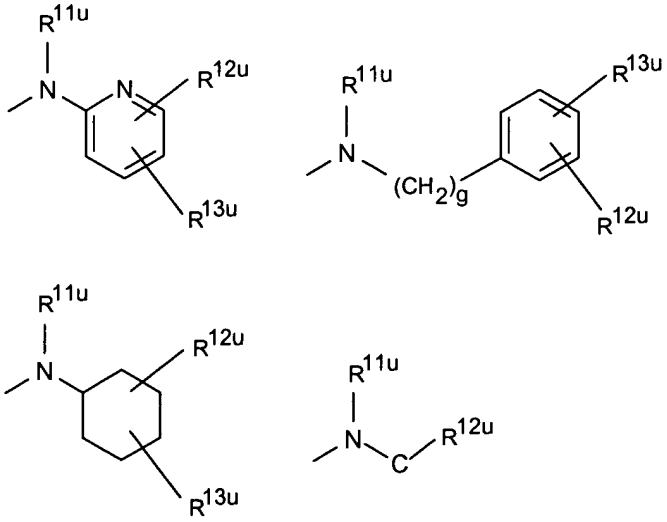




wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is -OH, $-NHR^{20u}$ or C_{1-6}-alkoxy wherein R^{20u} is hydrogen or C_{1-6}-alkyl; and

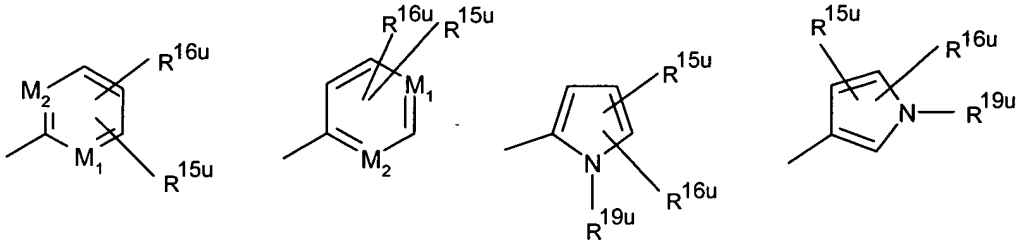
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14u} is hydrogen or C_{1-6}-alkyl; and

C is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; and

.... is optionally a single bond or a double bond; and

R^{18u} is selected from



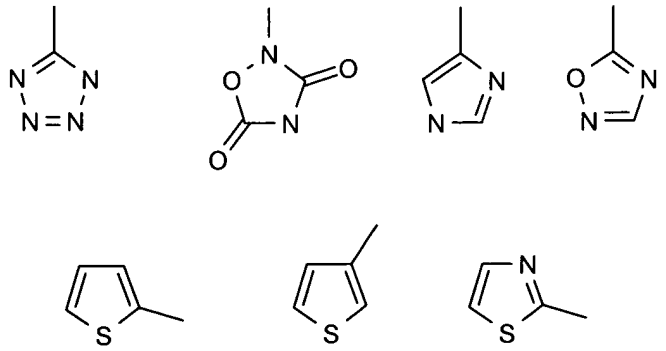
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(2R)-piperidinecarboxylic acid;

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2Z)-butenyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propionyl)-(3R)-piperidine-carboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidine-carboxylic acid;

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2E)-butenyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxopropyl)-(3R)-piperidinecarboxylic acid;

1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butynyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-dibenzo[b,f]azepin-5-ylmethyl)-1-pentyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Trifluoromethyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(3-Methoxy-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(3-(2-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-(3R)-piperidinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-1-piperazinyl)-nicotinic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopropylmethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-cyclopentylmethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-ethyl)-(3R)-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-3-oxopropyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(4-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-butyn-1-yl)-3-piperidinecarboxylic acid

(R)-1-((2R)-Methyl-3-(3-methyl-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)1-methylpropyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-methyl-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidine-carboxylic acid;

(R)-1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methyl-1-propyl)-3-pyrrolidinylacetic acid;

2-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperazinyl)-nicotinic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-1-pentyl)-3-piperidinecarboxylic acid;

2-(4-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)piperazin-1-yl)nicotinic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-methyl-3-oxo-propyl)-3-piperidinearboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylcarbonyl)-1-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-benzyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-3-oxo-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-(2R)-methylpropyl)-4-piperidine-carboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxy-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-hydroxypropyl)-3-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-2-propoxypropyl)-4-piperidinecarboxylic acid;

(R)-1-(2-(N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-N-methylamino)ethyl)-

3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy or methylthio, $-NR^7R^8$ or $-SO_2NR^7R^8$ wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl ; and

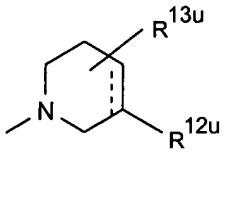
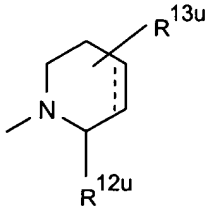
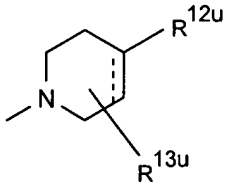
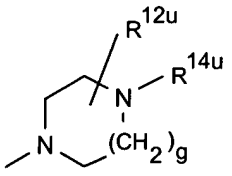
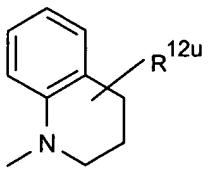
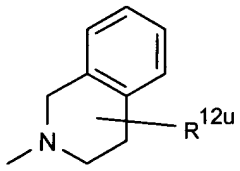
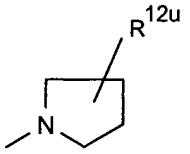
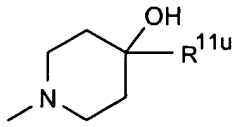
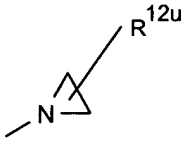
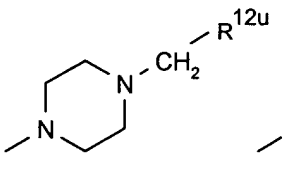
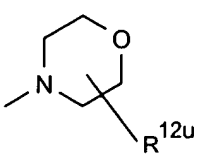
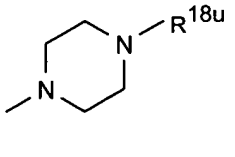
Y is >CH-O- or >CH-$S(O)_y$ wherein y is 0, 1 or 2, or $-N(R^8)-$ wherein R^8 is hydrogen or C_{1-6}-alkyl; and

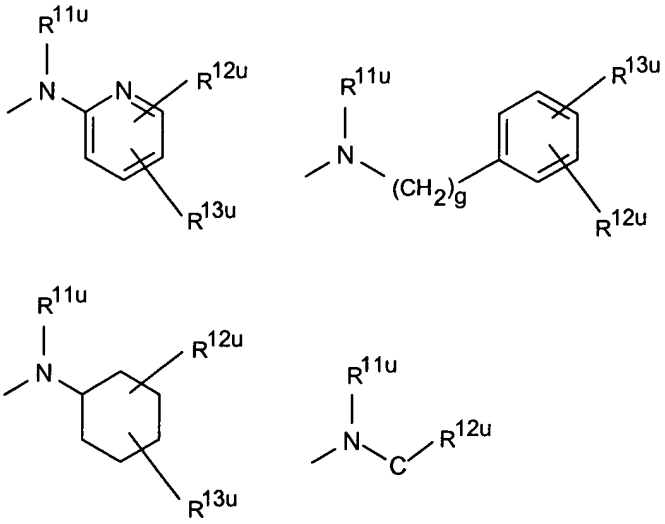
X is completion of an optional bond, ortho-phenylene, -O-, -S-, $-C(R^7R^8)-$, $-CH_2CH_2-$, -CH=CH-CH_2-, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-N(R^8)-(C=O)-$, $-(C=O)-N(R^8)-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-CH_2OCH_2-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^8)-$, $-N(R^8)(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^9)CH_2-$, $-CH_2CH(R^9)-$, -(C=O)-, $-N(R^8)-$ or $-(S=O)-$ wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q independently are 0 or 1; and

r is 1, 2, 3 or 4; and

Z is selected from



wherein g is 0, 1 or 2; and

R^{11u} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{12u} is $-(CH_2)_hOH$ or $-(CH_2)_jCOR^{17u}$ wherein h is 0, 1, 2, 3, 4, 5 or 6 and j is 0 or 1 and wherein R^{17u} is -OH, $-NHR^{20u}$ or C_{1-6}-alkoxy wherein R^{20u} is hydrogen or C_{1-6}-alkyl; and

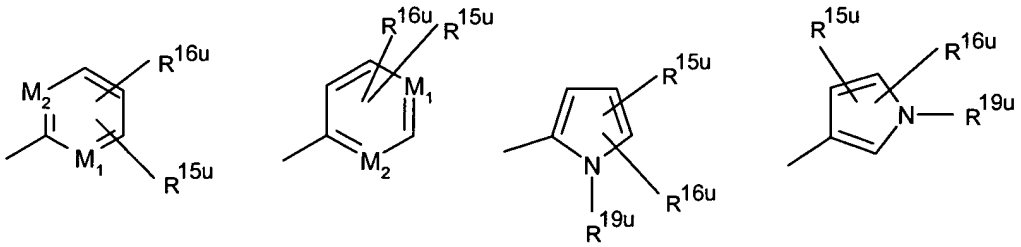
R^{13u} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14u} is hydrogen or C_{1-6}-alkyl; and

C is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene; and

.... is optionally a single bond or a double bond; and

R^{18u} is selected from



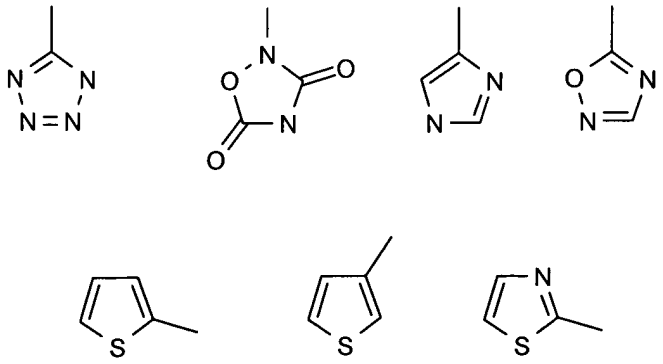
wherein M_1 and M_2 independently are C or N; and

R^{19u} is hydrogen, C_{1-6}-alkyl, phenyl or benzyl; and

R^{15u} is hydrogen, halogen, trifluoromethyl, nitro or cyano; and

R^{16u} is hydrogen, halogen, trifluoromethyl, nitro, cyano, $-(CH_2)_kCOR^{17u}$, $-(CH_2)_kOH$ or $-(CH_2)_kSO_2R^{17u}$ wherein k is 0, 1 or 2; or

R^{16u} is selected from



or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-

piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

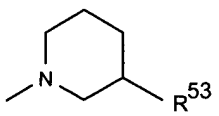
Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; and

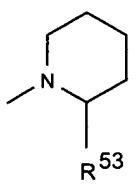
X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N(CH_3)SO_2-, -SO_2N(CH_3)-, -CH(R^9)CH_2-, -CH_2CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

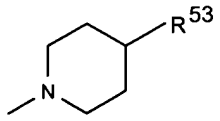
p and q are 0; and

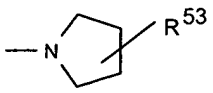
r is 1, 2 or 3; and

Z is selected from









wherein R^{53} is -(CH_2)$_{pp}$COOH wherein pp is 2, 3, 4, 5 or 6; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

3-(1-(3-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(3-(10,11-Dihydrodibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(2-(10,11-Dihydrodibenzo[a,d]cyclohepten-5-ylidene)ethyl)piperidin-4-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(Xanthen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)-butyric acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-2-yl)-propionic acid;

3-(1-(3-(1-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Fluoro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Trifluoromethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

3-(1-(3-(2-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Methoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-piperidin-4-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(2-Fluoro-6,11-dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)-propionic acid;

4-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)butyric acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-3-yl)propionic acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-2-yl)propionic acid;

3-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-propionic acid;

4-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)-butyric acid;

3-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)pyrrolidin-3-yl)propionic acid;

3-(1-(3-(10H-Anthracen-9-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

3-(1-(3-(Dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)piperidin-4-yl)propionic acid;

5-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(6,11-Dihydro-dibenz[b,e]thiepin-11-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(Thioxanthen-9-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid;

5-(1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)piperidin-4-yl)pentanoic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

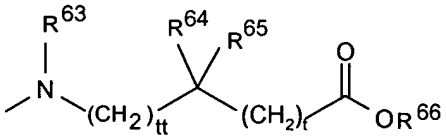
Y is >N-CH_2- , >CH-CH_2- , >C=CH- or >CH-O- wherein only the underscored atom participates in the ring system; and

X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -S-CH_2-, -CH_2-S-, -$(CH_2)N(R^8)$-, -N(R^8)(CH_2)-, -$N(CH_3)SO_2$-, -$SO_2N(CH_3)$-, -CH(R^9)CH_2-, -$CH_2CH(R^9)$-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q are 0; and

r is 1, 2 or 3; and

Z is



wherein tt and t independently are 0, 1 or 2; and

R^{63} is H, C_{1-6}-alkyl or optionally substituted benzyl;

R^{64} and R^{65} independently are H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, phenyl, thienyl, benzyl, or R^{64} and R^{65} together with the C-atom they are attached to form a 3 - 8 membered carbocyclic ring; and

R^{66} is H or C_{1-6}-alkyl; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidinecarboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

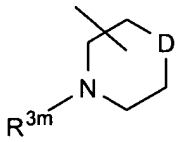
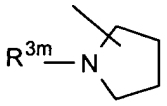
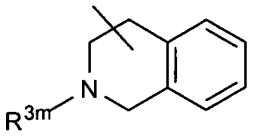
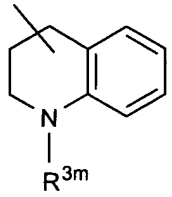
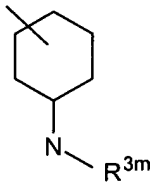
Y is >N-CH_2- , >CH-CH_2- or >C=CH- wherein only the underscored atom participates in the ring system; and

X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N(CH_3)SO_2-, -SO_2N(CH_3)-, -CH(R^9)CH_2-, -CH_2CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q are 0; and

r is 0, 1 or 2; and

Z is selected from

wherein D is -CH_2-, -O-, -S- or -N(R^7)- wherein R^7 is H or C_{1-6}-alkyl; and

R^{3m} is -$(CH_2)_{mm}$OH or -$(CH_2)_{mp}$COR^4 wherein mm and mp are 1, 2, 3 or 4 and R^4 is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

3-(3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-pyrrolidin-1-yl)-propionic acid;

(2-(2-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-ylmethyl)-morpholin-4-yl)-acetic acid;

(3-(10,11-Dihydro-5H-dibenz[(b,f]azepin-5-ylmethyl)-1-piperidyl)acetic acid.

In another preferred embodiment of the invention in formula Ia

R^1, R^{1a}, R^2 and R^{2a} independently are hydrogen, halogen, cyano, trifluoromethyl, methylthio, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

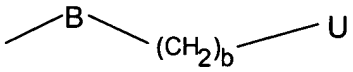
Y is >N-, >CH-, >N-(C=O)- or >C=C(R^8)-, wherein only the underscored atom participates in the ring system and R^8 is hydrogen or C_{1-6}-alkyl; and

X is ortho-phenylene, -O-, -S-, -C(R^7R^8)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, -$CH_2CH_2CH_2$-, -CH=CH-, -N(R^8)-(C=O)-, -(C=O)-N(R^8)-, -O-CH_2-, -CH_2-O-, -OCH_2O-, -CH_2OCH_2-, -S-CH_2-, -CH_2-S-, -(CH_2)N(R^8)-, -N(R^8)(CH_2)-, -N$(CH_3)SO_2$-, -$SO_2N(CH_3)$-, -CH(R^9)CH_2-, -CH_2CH(R^9)-, -(C=O)-, -N(R^8)- or -(S=O)- wherein R^7 and R^8 independently are hydrogen or C_{1-6}-alkyl; and wherein R^9 is C_{1-6}-alkyl or phenyl; and

p and q are 0; and

r is 0, 1, 2, 3 or 4; and

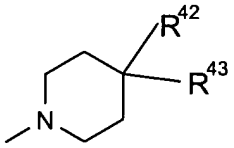
Z is



wherein b is 0, 1, 2, 3 or 4; and

B is -CH=CR^{49}-, -CR^{49}=CH-, -C≡C-, -(C=O)-, -(C=CH_2)-, -(C$R^{49}R^{40}$)-, -CH(OR^{41})-, -CH(NHR^{41})-, phenylene, C_{3-7}-cycloalkylene or the completion of a bond, wherein R^{49} and R^{40} independently are hydrogen, C_{1-6}-unbranched alkyl, C_{3-6}-branched alkyl or C_{3-7}-cycloalkyl and wherein R^{41} is hydrogen or C_{1-6}-alkyl; and

U is



wherein R^{42} is hydrogen, -$(CH_2)_c$OH or -$(CH_2)_d$COR^{47} wherein c is 0, 1, 2, 3, 4, 5 or 6 and d is 0 or 1 and wherein R^{47} is -OH, -NHR^{44} or C_{1-6}-alkoxy wherein R^{44} is hydrogen or C_{1-6}-alkyl; and

R^{43} is cyano, -$NR^{45}R^{46}$, -NR^{45}-V or -$(CHR^{48})_e$-V wherein R^{45} and R^{46} independently are hydrogen or C_{1-6}-alkyl and wherein e is 0, 1, 2, 3, 4, 5 or 6 and wherein R^{48} is hydrogen, halogen, cyano, trifluoromethyl, hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, -$NR^{45}R^{46}$ or -COOH, and

wherein V is C_{3-8}-cycloalkyl, aryl or heteroaryl, which rings may optionally be substituted with one or more halogen, cyano, trifluoromethyl, hydroxy, methylthio, C_{1-6}-alkyl or C_{1-6}-alkoxy; or a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-phenyl-4-piperidinecarboxylic acid;

4-(4-Chlorophenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

4-(4-Methylphenyl)-1-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-anilino-4-piperidinecarboxamide;

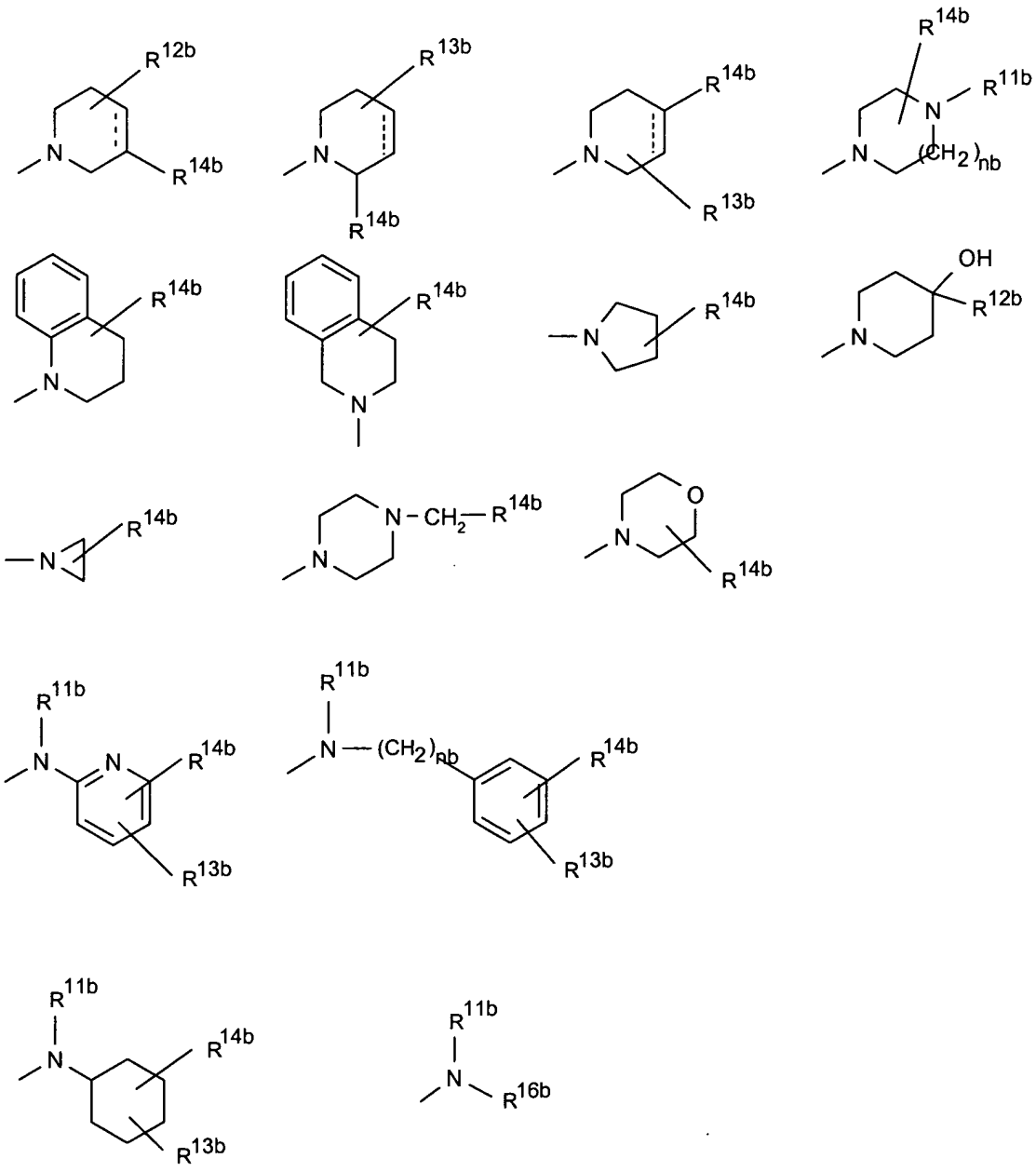
2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidyl)-2-phenylacetonitrile;

2-(1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-piperidinyl)-2-phenylacetic acid;

1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-4-cyano-4 piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ib

R^{1b} and R^{2b} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and
R^{3b} is hydrogen or C_{1-3}-alkyl; and
A_b is C_{1-3}-alkylene; and
Y_b is >$\underline{C}$H-CH_2-, >$\underline{C}$=CH-, >$\underline{C}$H-O-, >$\underline{C}$=N-, >$\underline{N}$-CH_2- wherein only the underscored atom participates in the ring system; and
Z_b is selected from



wherein nb is 1 or 2; and

R^{11b} is hydrogen or C_{1-6}-alkyl; and

R^{12b} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or phenyl optionally substituted with halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{13b} is hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{14b} is $-(CH_2)_{mb}OH$ or $-(CH_2)_{tb}COR^{15b}$ wherein mb is 0, 1, 2, 3, 4, 5 or 6 and tb is 0 or 1 and wherein R^{15b} is -OH, NH_2, -NHOH or C_{1-6}-alkoxy; and

R^{16b} is C_{1-6}-alkyl or -B_b-COR^{15b}, wherein B_b is C_{1-6}-alkylene, C_{2-6}-alkenylene or C_{2-6}-alkynylene and R^{15b} is the same as above; and

... is optionally a single bond or a double bond; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-3-piperidinecarboxylic acid ethyl ester;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-4-piperidinecarboxylic acid;

(R)-1-(3-(2,10-Dichloro-12H-dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

1-(3-(2,10-Dichloro-12H-dibenzo[d,g[1,3]dioxocin-12-ylidene)-1-propyl)-3-pyrrolidineacetic acid;

(R)-1-(2-(12H-Dibenzo[d,g][1,3]dioxocin-12-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,10-Dichloro-12H-dibenzo[d,g][1,3]dioxocin-12-yloxy)-1-ethyl)-3-piperidinecarboxylic acid;

(R)-1-(3-(2-Chloro-12H-dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-3-piperidinecarboxylic acid;

1-(3-(12H-Dibenzo[d,g][1,3,6]dioxazocin-12-yl)-1-propyl)-4-piperidinecarboxylic acid;

2-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(2-dimethylamino)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(3-dimethylamino)propyl-12H-dibenzo[d,g][1,3]dioxocine;

2,10-Dichloro-12-(3-dimethylamino-1-methyl)ethoxy-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(2-dimethylaminopropylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-dimethylamino-1-methylpropylidene)-12H-dibenzo-[d,g][1,3]dioxocine;

2-Fluoro-12-(3-dimethylamino)propylidene-12H-dibenzo[d,g][1,3]dioxocine;

2-Methyl-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

2-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

3-Chloro-12-(3-(4-methyl-1-piperazinyl)propylidene)-12H-dibenzo[d,g][1,3]dioxocine;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid ethyl ester;

1-(3-(12H-Dibenzo[d,g][1,3]dioxocin-12-ylidene)propyl)-3-piperidinecarboxylic acid.

In another preferred embodiment of the invention in formula Ic

R^{1c} and R^{2c} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

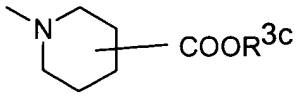
X_c is ortho-phenylene, -O-, -S-, $-C(R^{6c}R^{7c})-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-N(R^{8c})-(C=O)-$, $-(C=O)-N(R^{8c})-$, $-O-CH_2-$, $-CH_2-O-$, $-OCH_2O-$, $-S-CH_2-$, $-CH_2-S-$, $-(CH_2)N(R^{8c})-$, $-N(R^{8c})(CH_2)-$, $-N(CH_3)SO_2-$, $-SO_2N(CH_3)-$, $-CH(R^{10c})CH_2-$, $-CH_2CH(R^{10c})-$, -(C=O)-, $-N(R^{9c})-$ or -(S=O)- wherein R^{6c}, R^{7c}, R^{8c} and R^{9c} independently are hydrogen or C_{1-6}-alkyl, and wherein R^{10c} is C_{1-6}-alkyl or phenyl; and

Y_c is C or N; and

.... is optionally a single bond or a double bond, and .... is a single bond when Y_c is N; and

mc is 1, 2, 3, 4, 5 or 6; and

Z_c is $-COOR^{3c}$ or



wherein R^{3c} is H or C_{1-6}-alkyl;or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

1-(2-(10,11-Dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-(3R)-piperidinecarboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-4-piperidine-carboxylic acid;

1-(2-(2-Methyl-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(8-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

1-(2-(8-Methylthio-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)-1-ethyl)-3-piperidine-carboxylic acid;

(R)-1-(2-(10,11-Dihydrodibenzo[b,f]oxepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-10,11-dihydrodibenzo[b,f]thiepin-10-ylsulfanyl)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(11H-Dibenz[b,f][1,4]oxathiepin-11-ylmethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid;

(R)-1-(2-(2,4-Dichloro-10,11-dihydrodibenzo[b,f]thiepin-10-yloxy)ethyl)-3-piperidinecarboxylic acid.

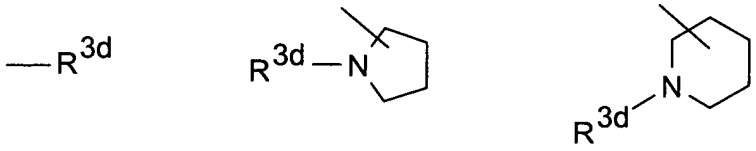
In another preferred embodiment of the invention in formula Id

R^{1d} and R^{2d} independently are hydrogen, halogen, trifluoromethyl, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

X_d is -O-, -S- or -S(=O)-; and

rd is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 ; and

Z_d is selected from



wherein R^{3d} is $-(CH_2)_{md}OH$ or $-(CH_2)_{pd}COR^{4d}$ wherein md and pd independently are 0, 1, 2, 3 or 4 and R^{4d} is OH, NH_2, NHOH or C_{1-6}-alkoxy; or

a pharmaceutically acceptable salt thereof.

Further preferred compounds of the invention include:

4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]oxazepin-2-yl)-butanoic acid;

4-(1,3,4,14b-Tetrahydro-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]thiazepin-2-yl)-butanoic acid.

The compounds of general formulas Ia-Id may be prepared by using the methods taught in WO9631497, WO9631498, WO9631499, WO9631481, WO9711071, WO9815548, WO9815546, WO9815550, PCT/DK98/00273, PCT/DK98/00271, DK 0367/98, DK 0366/98, DK 1472/97 and DK 1523/98, which are hereby incorporated by reference.

It has been demonstrated that the compounds of the present the invention can be used in the treatment of conditions related to angiogenesis according to the following experiment.

PHARMACOLOGICAL METHODS

The effects of compounds of formulas Ia-Id on angiogenesis are suggested by the following experiments. Air pouches were formed on the dorsum of female To mice and were inflamed one day later by injection of 0.5 ml Freund's complete adjuvant supplemented with 0.1% croton oil. Animals were dosed with compounds of formulas Ia-Id given via the drinking water equivalent to 3-30 mg/kg/day. Control animals received normal drinking water. After 6 days the animals received an injection of carmine in gelatine intravenously prior to dissection of the air pouch granuloma. Comparisons of granuloma dry weight, carmine content and vascular index (carmine content/granuloma dry weight) were made between the groups (Colville-Nash et al., J. Pharmacol. Exp. Ther. 274 1463-1472, 1995).

Treatment with compounds of formulas Ia-Id during 6 days gave reductions in the vascular index between 27-36%

Neovascularization in mouse corneas was induced by surgical implantation of a micropellet containing VEGF (vascular endothelial growth factor) or FGF (fibroblast growth factor) 0.6-0.8mm from the corneal limbus. Animals were dosed with compounds of formulas Ia-Id given via the drinking water equivalent to 15 mg/kg/day. After 5 days the stimulation of new blood vessel growth was examined by measuring the vessel length and vessel area (Cao et al., J. Clin. Invest. 98, 2507-2511, 1996).

Treatment with compounds of formulas Ia-Id resulted in a decrease of the vessel area of neovascularization of 30-50%.

PHARMACEUTICAL COMPOSITIONS

The present invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds according to the invention or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions comprising a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, syrup, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, topical, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a

liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound according to the invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 g
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of indications

related to angiogenesis. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, in an effective amount.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of humans, dosages from about 0.1 to about 1000 mg, preferably from about 0.5 to about 500 mg of compounds of formula I, conveniently given from 1 to 5 times daily. A most preferable dosage is from about 50 to about 200 mg per dose when administered to e.g. a human. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 50 to about 200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.1 mg to about 1000 mg, preferably from about 0.5 mg to about 500 mg of the compounds according to the invention admixed with a pharmaceutically acceptable carrier or diluent.

The method of treating may be described as the treatment, prevention, elimination, alleviation or amelioration of a condition related to angiogenesis in a subject in need thereof, which comprises the step of administering to the said subject an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Any novel feature or combination of features described herein is considered essential to this invention.